Complete Summary

GUIDELINE TITLE

2002 national guideline on the management of the viral hepatitides A, B, and C.

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline on the management of the viral hepatitides A, B, and C. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [201 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Viral hepatitides A, B, and C

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present a national guideline on the management of viral hepatitides A, B, and C

TARGET POPULATION

Patients in the United Kingdom with:

- Hepatitis A
- Hepatitis B
- Hepatitis C

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis of Viral Hepatitis A

1. Assessment of clinical features
2. Serology: serum hepatitis A virus specific immunoglobulin M (IgM)
3. Other diagnostic tests
    - Serum/plasma aminotransferases
    - Bilirubin
    - Alkaline phosphatase levels
    - Prothrombin time

Assessment/Diagnosis of Viral Hepatitis B

1. Assessment of clinical features
2. Hepatitis B serology
    - Surface antigen
    - "e" antigen
    - Immunoglobulin M (IgM) anti-core antibody
    - Immunoglobulin G (IgG) anti-core antibody
    - Hepatitis B virus deoxyribonucleic acid (DNA)
    - Antibody to hepatitis B e antigen (anti-HBe)
    - Antibody to hepatitis B surface antigen (anti-HBs)
    - Antibody to hepatitis B core antigen (anti-HBc)
3. Other diagnostic tests
    - Serum/plasma aminotransferases
    - Bilirubin
    - Alkaline phosphates levels
    - Prothrombin time
    - For chronic infection, aminotransferase levels and liver function tests

Assessment/Diagnosis of Viral Hepatitis C

1. Assessment of clinical features
2. Serology

- A screening antibody test: enzyme-linked immunoassay, recombinant immunoblot assay
- Molecular biological techniques such as a reverse transcription-polymerase chain reaction (RT-PCR) assay for viral ribonucleic acid (RNA)

3. Other diagnostic tests
    - Acute infection, as for hepatitis A
    - Chronic infection, as for hepatitis B

Management/Treatment of Viral Hepatitis A

1. General advice and patient education
2. Screening for other sexually transmitted infections in cases of sexually acquired hepatitis
3. Criteria for inpatient or outpatient treatment in acute icteric hepatitis
4. Considerations for pregnant and breastfeeding women
5. Management of sexual contacts and other contacts
    - Partner notification
    - Human normal immunoglobulin
    - Hepatitis A vaccine
6. Follow-up
7. Primary prevention: vaccination recommendations and education

Management/Treatment of Viral Hepatitis B

1. General advice and patient education
2. Screening for other sexually transmitted diseases in cases thought to have been sexually acquired or otherwise appropriate
3. Liver biopsy for assessment of chronic disease
4. Criteria for inpatient or outpatient treatment in acute icteric hepatitis (same as hepatitis A)
5. Pharmacotherapy for chronic infection
    - Alpha interferon therapy
    - Lamivudine
    - Famciclovir
    - Adefovir
    - Thymosin alpha
    - Ribavirin
6. Considerations for pregnant and breastfeeding women
7. Management of sexual contacts and other contacts
    - Partner notification, contact tracing, screening, and education
    - Hepatitis B immunoglobulin
    - Accelerated course of recombinant vaccine
8. Follow-up
9. Screening and primary prevention activities, such as vaccination

Management/Treatment of Viral Hepatitis C

1. General advice and patient education
2. Pharmacotherapy: alpha and/or beta interferon, ribavirin, consensus interferon, pegylated interferon, ketoprofen, amantadine
3. Vaccination against hepatitis A and B

4. Considerations for pregnant and breastfeeding women
5. Management of sexual contacts and other contacts: partner notification and contact tracing
6. Follow-up
7. Screening and primary prevention
    - Testing for hepatitis C
    - Needle and syringe exchange schemes

MAJOR OUTCOMES CONSIDERED

- Rates of infection of viral hepatitis A, B, and C
- Morbidity and mortality due to viral hepatitis A, B, or C infection and complications of infection

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

For each type of hepatitis, the guideline developers performed a Medline (U.S. National Library of Medicine) search for the years 1966-2000 (June) for hepatitis types A and B and 1990-2000 (June) for hepatitis C. From the Medical Subject Headings (MeSH) terms "hepatitis A", "hepatitis B", and "hepatitis C", the following subheadings were used: Complications, Drug Therapy, Diagnosis, Epidemiology, Etiology, Mortality, Prevention and Control, Therapy, Transmission, Virology. The searches were limited to "human" for all searches. For Drug Therapy, Prevention and Control, and Therapy searches were limited initially to "randomized controlled trials" but in the absence of enough publications this was changed to "controlled clinical trials", "clinical trials", or "reviews" in that order. For the subheadings other than these three the search was limited to "reviews". Textword searches for "hepatitis A", "hepatitis B", and "hepatitis C" were combined, as appropriate, with textword searches for "complication$", "diagnosis", "prevention", "transmission", "immunoglobulin", "vaccine", "non-response", "non-responders", "HIV", "randomized controlled trial", "lamivudine", "famciclovir", "ribavirin".

The Cochrane Library 2000 v2 (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Cochrane Clinical Trial Register) was searched for all relevant articles using the textword "hepatitis".

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial versions of the guidelines were sent for review to the following:

- Clinical Effectiveness Group (CEG) members
- Chairs of UK Regional GU Medicine Audit Committees who had responded to an invitation to comment on them
- Chair of the Genitourinary Nurses Association (GUNA)
- President of the Society of Health Advisers in Sexually Transmitted Diseases (SHASTD)
- Clinical Effectiveness Committee of the Faculty of Family Planning and Reproductive Health Care (FFP)

Comments were relayed to the authors and attempts made to reach a consensus on points of contention with ultimate editorial control resting with the Clinical Effectiveness Group. Finally, all the guidelines were ratified by the councils of the two parent societies.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (I-IV) and grades of recommendation (A-C) are repeated at the end of the "Major Recommendations" field.

Hepatitis A Virus Infection

Diagnosis

Serology

Confirmed by a positive serum hepatitis A virus (HAV) specific immunoglobulin M (IgM) that remains positive for 6 months or more (McPherson, 1994; Liaw et al., 1986). Hepatitis A virus - immunoglobulin G (IgG) does not distinguish between current or past infection and may remain positive for life (McPherson, 1994; Stapleton, 1995).

Other tests

- Serum/plasma aminotransferases (AST/ALT) 500-10,000 IU/l. Bilirubin up to 500 micromoles/l. Alkaline phosphatase levels < 2x the upper limit of normal, but higher if there is cholestasis (McIntyre, 1990; Fagan & Williams, 1990; Willner et al., 1998; Vento et al., 1998).
- Prothrombin time (PT) prolongation by more than 5 seconds suggests developing hepatic decompensation (McIntyre, 1990; Fagan & Williams, 1990).

Management

General advice

- Patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (level of evidence III, grade of recommendation B) (Maguire et al., 1995; Shapiro & Margolis, 1993; Minuk et al., 1994; Massoudi et al., 1999; Oxman et al., 1994).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Hepatitis A is a notifiable disease.

Further investigation

Screen for other sexually transmitted infections in cases of sexually-acquired hepatitis or if otherwise appropriate.

Acute icteric hepatitis

- Mild/moderate (80%), manage as an outpatient emphasising rest and oral hydration (III, B) (McIntyre, 1990).
- Severe attack with vomiting, dehydration, or signs of hepatic decompensation (change in conscious level or personality); admit to hospital (III, B) (Fagan & Williams, 1990; Willner et al., 1998).

Pregnancy and breast feeding

- Pregnant women should be advised of the increased risk of miscarriage/premature labor and the need to seek medical advice if this happens (Medhat et al., 1993).
- Breast-feeding can be continued but consider giving human normal immunoglobulin (HNIG) 125 mg intramuscularly (IM) to the baby, although most children will have mild or asymptomatic infection (IV, C) (Salisbury & Begg, 1996).

Sexual and other contacts

- Partner notification should be performed for at risk homosexual contacts (oro/anal, digital/rectal, and penetrative anal sex) within the period 2 weeks before to 1 week after the onset of jaundice. This to be documented and the outcome documented at subsequent follow-up. Other people thought to be at risk (household contacts, those at risk from food/water contamination) to be contacted via the public health authorities (consultant in communicable disease control [CCDC] or equivalent). The consultant in communicable disease control has a duty of confidentiality to the index patient.
- Human normal immunoglobulin, 250-500 mg intramuscularly, should be considered for close household and sexual contacts who are not known to be immune (but see below) (Ib, A) (Salisbury & Begg, 1996; Winokur & Stapleton, 1992).
- Human normal immunoglobulin works best if given in the first few days after first contact with an efficacy of 90% and is unlikely to give any protection more than 2 weeks after first exposure. Remember, patients are most infectious for 2 weeks before the jaundice (that is, before the illness is recognised).
- Hepatitis A vaccine may also be given after exposure (IIa, B) (Salisbury & Begg, 1996; Irwin & Millership, 1999; Mele, 1999).
- Hepatitis A vaccine schedule: doses at 0 and 6-12 months, 95% protection for at least 5 years (Ib, A) (Dagan et al., 1999; Lu et al., 1999; Vidor et al., 1998; Chan et al., 1999). Revaccinate after 10 years (IIb, B) (Dagan et al., 1999; Lu et al., 1999; Vidor et al., 1998; Chan et al., 1999; Hess et al., 1995; Neilsen, Bodsworth, & Watts, 1997; Thompson & Norris, 1998). Human immunodeficiency virus (HIV)-positive patients respond (antibody production) in 73-88% but titres are lower than in HIV-negative individuals (IIa, B) (Hess et al., 1995; Neilson, Bodsworth, & Watts, 1997). There is a combined hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (IIa, B) (Thompson & Norris, 1998; Frey et al., 1999).
- If an outbreak is suspected or if the index case is a food handler, notify the local consultant in communicable disease control by telephone (IV, C) (Salisbury & Begg, 1996).

Follow-up

- See at 1 or 2 weekly intervals until aminotransferase levels are normal (usually 4-12 weeks) (IV, C).
- Immunity is lifelong. (McPherson, 1994; Stapleton, 1995)

Primary prevention

- Current evidence still suggests that most gay men are not at increased risk for hepatitis A infection (Villano et al., 1997; Nandwani et al., 1994; Corona et al., 1999) and therefore universal vaccination in this group cannot be firmly recommended (III, B). However, many outbreaks have been reported amongst gay men in large cities and therefore clinics in these areas (e.g. central London) should offer vaccination, particularly when increased rates of infection in gay men have been recognised locally (III, B) (Stewart & Crofts, 1993; Leentvaar-Kuijpers et al., 1995; Anon, 1997; Walsh et al., 1996; Villano et al., 1997; Reintjes et al., 1999; Ferson, Young, & Stokes, 1998; Salisbury & Begg, 1996).
- Evidence is accumulating that intravenous drug users and patients with chronic hepatitis C infection should also be vaccinated (III, B) (Grinde et al., 1997; Shaw et al., 1999; Stene-Johansen et al., 1998; Vento et al., 1998; Salisbury & Begg, 1996).
- Vaccination is also recommended for travellers to developing countries, people with haemophilia or chronic liver disease, those with occupational exposure, and for people at risk in an outbreak (Ib, A) (Salisbury & Begg, 1996).
- Health/sex education should stress the routes of transmission and the higher incidence in developing countries (IV, C) (Salisbury & Begg, 1996).

Hepatitis B Virus Infection

Diagnosis

See Table 1

Table 1. Hepatitis B Serology (McPherson, 1994; Hoofnagle, 1990; Gitlin, 1997)

Stage of infection	Surface antigen (HBsAg	"e" antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti HBs
Acute (early)	+	+	+	+	+	-	-
Acute (resolving)	+	-	+	+	-	+/-	-
Chronic (high infectivity)	+	+/-	-	+	+	-	-

Stage of infection	Surface antigen (HBsAg	"e" antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti HBs
Chronic (low infectivity)	+	-	-	+	-	+/-	-
Resolved (immune)	-	-	-	+	-	+/-	+/-
Successful vaccination	-	-	-	-	-	-	+

Other tests

- Acute infection, see hepatitis A.
- Chronic infection, in most cases the only abnormality to be found will be mildly abnormal aminotransferase levels (usually <100 IU/l) and in many the liver function tests will be normal. Only in severe late stage liver disease do the liver function tests become grossly abnormal (Hoofnagle, 1990; Gitlin, 1997; Brook et al., 1989; Brook et al., 1989; Brook, Karayiannis, & Thomas, 1989; Nevens et al., 1997).

Management

General advice

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact, until they have become non-infectious or their partners have been successfully vaccinated (see below) (III, B) (Davis et al., 1989; Hoofnagle, 1990; Struve et al., 1990; Salisbury & Begg, 1996; el-Dalil et al., 1995).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s), routes of transmission of infection (see below) and advised not to donate blood (IV, C) (Salisbury & Begg, 1996).
- Hepatitis B is a notifiable disease.

Further investigations

Screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate (IIb, B) (Hart et al., 1993; Hyams, Phillips, & Tejada, 1990).

Other tests such as liver biopsy (for assessment of chronic disease) should be performed only by specialists in this field (IV, C) (Hoofnagle, 1990; Gitlin, 1997; Brook et al., 1989; Brook et al., 1989; Brook, Karayiannis, & Thomas, 1989; Nevens et al., 1997).

Acute icteric hepatitis

As for hepatitis A.

Treatment of chronic infection

- Patients should be considered for alpha interferon therapy, 5-20 M.U. thrice weekly for twelve to thirty two weeks (Ib, A) (Brook et al., 1989; Brook et al., 1989; Brook, Karayiannis, & Thomas, 1989; Janssen et al., 1999; Carreno et al., 1999). Additional promising treatments, alone or in combination with interferon, include lamivudine (Ib, A), famciclovir (IIb, B), adefovir (IIb, B), thymosin alpha (Ib, A) and ribavirin (IIb, B) (Lai et al., 1997; Main et al., 1996; Dienstag et al., 1999; Marques et al., 1998; Tsiang et al., 1999; Cotonat et al., 2000; Chien et al., 1998). Response to interferon is highest (40-50%) in patients with adult-acquired infection with inflammatory liver disease who are not immunocompromised (Ib, A) (Brook et al., 1989; Brook et al., 1989; Brook, Karayiannis, & Thomas, 1989). Interferon treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer (Ikeda et al., 1998; Lin et al., 1999).
- Lamivudine and famciclovir will suppress hepatitis B viral replication during therapy of immunocompromised patients, including those with HIV, and may delay liver damage (IIb, B) (Thibault et al., 1999; Dore et al., 1999; Rayes et al., 1999). Cure is unusual in these patients, anti-viral resistance often develops after prolonged monotherapy and rebound hepatitis can occur if the agent is stopped or if resistance ensues (IIb) (Thibault et al., 1999; Xiong et al., 2000).
- Specific therapy is otherwise not indicated unless de-compensated liver disease ensues (IV, C) (Hoofnagle, 1990).

Pregnancy and breast feeding

- Vertical transmission (mother to infant) of infection occurs in 90% of pregnancies where the mother is hepatitis B e antigen positive and in about 10% of surface antigen positive, e antigen negative mothers. Most (>90%) infected infants become chronic carriers (Brook et al., 1989; Kiire, 1996; Andre & Zuckerman, 1994).
- Infants born to infectious mothers are vaccinated from birth, usually in combination with hepatitis B specific immunoglobulin, 200 IU intramuscularly (Ia, A) (Brook et al., 1989; Andre & Zuckerman, 1994). This reduces vertical transmission by 90%.
- Infected mothers should continue to breast feed as there is no additional risk of transmission (Michielsen & Van Damme, 1999).

Sexual and other contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual

contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (IV, C) (Oxman et al., 1994; Gilson et al., 1994; Sutherland & Tilzey, 1993). The infectious period is from 2 weeks before the onset of jaundice until the patient becomes surface antigen negative. In cases of chronic infection trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired. This may be impractical for periods of longer than 2 or 3 years. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (IV, C) (Salisbury & Begg, 1996). For screening of other non-sexual partners who may be at risk, discuss with the consultant in communicable disease control or equivalent.

- Specific hepatitis B immunoglobulin 500 IU intramuscularly hepatitis B immunoglobulin (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needlestick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than 7 days (Ib, A) (Salisbury & Begg, 1996; Anon, 1975).
- An accelerated course of recombinant vaccine should be offered to those given hepatitis B immune globulin (HBIG) plus all sexual and household contacts (at 0, 7, and 14 days or 0, 1, 2 months with a booster at 12 months in either course) (Ib, A) (Salisbury & Begg, 1996; Palmovich et al., 1993; Gilson et al., 1994; Sutherland & Tilzey, 1993; Jefferson et al., 1997; Francis et al., 1982; Nothdurft et al., 2002).
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-hepatitis B surface antigen titres >10 IU/l) (Ib, A) (Salisbury & Begg, 1996; Gilson et al., 1994; Sutherland & Tilzey, 1993; Francis et al., 1982).

Follow-up

- Acute infection: as for hepatitis A. In view of the possibility of chronic infection, serology should be repeated after 6 months even if the liver function tests are normal (Hoofnagle, 1990; Hyams, 1995; Gitlin, 1997).
- Chronic infection: if untreated, patients should be reviewed regularly at intervals of 1 year or less, ideally by a physician with expertise in this disease (IV, C) (Hoofnagle, 1990; Hyams, 1995).
- Immunity after recovery from infection (surface antigen negative) is lifelong in over 90%.

Screening and primary prevention

- Hepatitis B testing in asymptomatic patients should be considered in gay men, sex workers (of either sex), intravenous drug users, HIV-positive patients, sexual assault victims, people from countries where hepatitis B is common (outside of Western Europe, North America, and Australasia), needle-stick victims, and sexual partners of positive or high-risk patients (IV, C) (Ward, Day, & Weber, 1999; Salisbury & Begg, 1996; el-Dalil et al., 1995; Gilson et al., 1994; Sutherland & Tilzey, 1993). If non-immune, consider vaccination (see below) (Ib, A) (Salisbury & Begg, 1996; Palmovich et al., 1993; Jefferson et al., 1997; Francis et al., 1982). If found to be chronic carriers consider referral for therapy (Ia, A) (Brook et al., 1989; Brook et al.,

1989; Brook, Karayiannis, & Thomas, 1989; Nevens et al., 1997; el-Dalil et al., 1995; Janssen et al., 1999; Carreno et al., 1999; Lai et al., 1997; Main et al., 1996; Dienstag et al., 1999; Marques et al., 1998; Tsiang et al., 1999; Cotonat et al., 2000; Chien et al., 1998; Ikeda et al., 1998; Lin et al., 1999).

- The simplest initial screening test in someone who is unvaccinated or is of unknown infection status is anti-hepatitis B core antigen (anti-HBc), with the addition of other tests as necessary (III, B) (Allain et al., 1999; Gutierrez et al., 1999). Some units also screen for hepatitis B surface antigen (HBsAg) initially (IV, C) (el-Dalil et al., 1995; Gilson et al., 1994; Sutherland & Tilzey, 1993). Measure antibody to hepatitis B surface antigen (anti-HBs) in those who have been vaccinated.
- Vaccination should be offered to non-immune patients in most of the above groups (Ib, A) (Salisbury & Begg, 1996; Palmovich et al., 1993; Jefferson et al., 1997; Francis et al., 1982; Nothdurft et al., 2002). The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic carriage (IV, C) (el-Dalil et al., 1995; Gilson et al., 1994; Sutherland & Tilzey, 1993). HIV-positive patients show a reduced response rate to the vaccine (approximately 40%) and become antibody to hepatitis B surface antigen (anti-HBs) negative more quickly (IIb, B) (Wong et al., 1996; Tayal & Sankar, 1994; Rey et al., 2000).
- The vaccination schedules for both the monovalent and the combined hepatitis A+B vaccines are given below. The new ultra-rapid 0, 7, 14 day regimen offers the advantage of potentially higher uptake of the full course. Test for response (anti-HBs >10 IU/l, ideally >100 IU/l) 4-12 weeks after the last dose (Ib, A) (Salisbury & Begg, 1996; Palmovich et al., 1993; Jefferson et al., 1997; Francis et al., 1982). See above for the accelerated course. Non- or poor responders usually respond to further doses (up to three injections), ideally as a repeat course (Ib, A) with response rates up to 100% (Ib, A) (Clemens et al., 1997; Goldwater, 1997). New pre-S-containing vaccines are effective (Ib, A) and may also be used for conventional-vaccine non-responders (IIa, B) (Haubitz et al., 1996; Zuckerman et al., 1997; Heineman et al., 1999; Zuckerman, 1998; Eyigun et al., 1998).
- It is probable that booster doses of vaccine are not required for at least fifteen years in immunocompetent children and adults who have responded to an initial vaccine course (III, B) (European consensus group on hepatitis B immunity, 2000; Jack et al., 1999; Yuen et al., 1999; Wainwright et al., 1997). HIV-positive and other immunocompromised patients will still need to be monitored and given boosters when antibody to hepatitis B surface antigen (anti-HBs) levels fall below 100 IU./l (III, B) (Rey et al., 2000; European consensus group on hepatitis B immunity, 2000).
- Evidence suggests that if vaccine courses are not completed in immunocompetent patients, the outstanding doses can be given four or more years later without the need to restart a three dose course (III, B) (Wistrom et al., 1999). One or two doses of vaccine may provide immunity in 40% and over 90% of immunocompetent patients respectively (Wistrom et al., 1999; Marsano et al., 1998).

Vaccination Schedules for Hepatitis B using monovalent vaccine or combined A+B vaccine (Salisbury & Begg, 1996; Palmovich et al., 1993; Jefferson et al., 1997; Francis et al., 1982; Nothdurft et al., 2002)

Vaccination schedule: 0, 7, 14 days, 12 months

- Advantages
    - Rapid immunity
    - Short duration
    - High antibody titres at 12 and 13 months
    - Potential for better uptake
- Disadvantages
    - Not tested in HIV or other immunocompromised patients
    - Little published data
    - Low antibody titres in the first year (but current evidence suggests that protection is still adequate in the immunocompetent)

Vaccination schedule: 0, 1, 2, 12 months

- Advantages
    - Early immunity
    - Shorter time to early immunity than the 0, 1, 6 course
    - High antibody titres at 12 and 13 months
- Disadvantages
    - Antibody titres lower than the 0, 1, 6 in the first year

Vaccination schedule: 0, 1, 6 months

- Advantages
    - Higher antibody titres at 7 months than other two regimens, although this may not be clinically important
    - Long established regimen
    - Most researched in HIV
- Disadvantages
    - Poor uptake of the 6 month dose in the clinical setting

Hepatitis D (Delta virus infection, HDV)

This is an incomplete ribonucleic acid (RNA) virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of intravenous drug users (IVDUs) and their sexual partners but also is seen in female sex workers, and sporadically in other groups (Mele et al., 1988). Suspect hepatitis delta virus (HDV) infection in hepatitis B particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis, or if the liver disease in chronic hepatitis B virus is rapidly progressive (McIntyre, 1990; Fagan & Williams, 1990; Hoofnagle, 1990; Gitlin, 1997). There is a high rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis (McIntyre, 1990; Fagan & Williams, 1990; Hoofnagle, 1990). Diagnosis is confirmed by a positive - anti-HDV antibody or hepatitis delta virus - ribonucleic acid (HDV-RNA) test (McPherson, 1994; Gitlin, 1997). Response to anti-viral therapy is poor (Puoti et al., 1998; Lau et al., 1999).

Hepatitis C Virus Infection

Diagnosis

Serology

- A screening antibody test (usually an enzyme-linked immuno-assay, ELISA) is initially performed and if positive a second test, such as a recombinant immuno-blot assay (RIBA), is used to confirm infection (Polish et al., 1999; Colin et al., 1999; el-Dalil et al., 1995). Third generation enzyme-linked immuno-assay tests (ELISA-3) have an equivalent sensitivity to the recombinant immuno-blot assay (Mohan et al., 1999). Patients who are antibody positive on two occasions, six months apart, can be assumed to have chronic infection. Molecular biological techniques such as an reverse transcription-polymer chain reaction (RT-PCR) assay for viral ribonucleic acid are also available to confirm infection but are generally not required as 85-95% of recombinant immuno-blot assay/third generation enzyme-linked immuno-assay positive patients will be reverse transcription-polymer chain reaction positive (Dore, Kaldor, & McCaughan, 1997; Gretch, 1997; Lok & Gunaratnam, 1997; Mohan et al., 1999). The reverse transcription-polymer chain reaction does not reliably detect all hepatitis C virus (HCV) genotypes and is subject to inter-laboratory variability (Dore, Kaldor, & McCaughan, 1997; Gretch, 1997; Lok & Gunaratnam, 1997). Recent guidelines from the British Society of Gastroenterology suggest using RT-PCR as a confirmatory assay following an ELISA-3 positive test, although this strategy is not currently widely used due to cost and lack of evidence of cost-effectiveness. All patients being considered for therapy should have a viral RNA test to confirm viraemia (see below).

Other tests

- Acute infection, as for hepatitis A
- Chronic infection, as for hepatitis B

Management

General advice

- Patients should be told not to donate blood, semen, or organs and given advice on other routes of transmission (see below) (III, B) (Alter, 1997).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Acute hepatitis C infection is a notifiable disease.

Further investigations

As for hepatitis B.

Treatment

- Acute icteric hepatitis: there is some evidence that high dose alpha and/or beta interferon given during the acute phase will reduce the rate of chronicity to only 10% (IIb, B) (Vogel et al., 1996; Oketani et al., 1999; Takagi et al., 1998). Otherwise manage as for hepatitis A.

- Chronic infection: alpha interferon 3-10 MU intramuscularly thrice weekly given for 3-12 months will abolish chronic infection in approximately 20-30% of patients (Ia, A) (Davis & Lau, 1997; Schalm et al., 1997; Poynard et al., 1996; Niederau et al., 1996; Nomura et al., 1999; Ascione et al., 1998). The addition of ribavirin (1000-1200 mg/day) will increase the response rate to 35-50% (Ia, A) (Schalm et al., 1997; Reichard et al., 1998; McHutchinson et al., 1998; Poynard et al., 1998). Patients are more likely to respond if they have less severe liver disease (low fibrosis index on liver biopsy), low serum HCV-RNA levels (< 2 million RNA copies/ml), if they are infected with certain HCV sub-types (types 2 and 3) or if they become HCV-RNA in the serum within four weeks (Ib, A) (Davis & Lau, 1997; McHutchinson et al., 1998; Poynard et al., 1998; Davis et al., 1998; Martinot-Peignoux et al., 1998; Brouwer et al., 1998; Bellobueno et al., 1999; Kagawa et al., 1998; Montalto et al., 1998). HIV-positive patients respond well to treatment (IIa, B) (Soriano et al., 1995; Expert perspectives panel, 2000, 2001, 2002). Consensus interferon 9-15 micrograms thrice weekly and pegylated interferon 180 micrograms weekly also show promise (Ib, A) (Jensen et al., 1999; Zeuzem et al., 2000), as does the addition of ketoprofen (Ib, A) or amantadine (IIa, B) to the other agents (Munoz et al., 2000; Brillanti et al., 1999). For more information on therapy see the recent guidelines from the British Society of Gastroenterology.
- It is unclear whether chronically infected patients with a normal liver function test (tested on two occasions) should be treated. If they have liver damage demonstrated on biopsy, they will respond to therapy, but less well than patients with abnormal liver function tests (Ib, A) (Van Thiel et al., 1995; Sangiovanni et al., 1998).
- Given the high rate of fulminant hepatitis in co-infection hepatitis A and C and the worse prognosis of hepatitis B and C co-infection, patients with hepatitis C should be vaccinated against hepatitis A and B (III, B) (Vento et al., 1998; Satoglu et al., 1998; Mesquita, Granato, & Castelo, 1997).

Pregnancy and breast feeding

- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy (see transmission) (IV, C) (Dienstag et al., 1997).
- Breast feeding: there is no firm evidence of additional risk of transmission except, perhaps in women who are symptomatic with a high viral load (III, B) (Kumar & Shahul, 1998; Resti et al., 1998; Polywka et al., 1999)

Sexual and other contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (IV, C) (Oxman et al., 1994). The infectious period is from 2 weeks before the onset of jaundice in acute infection. If there was no acute infection trace back to the likely time of infection (for example, blood transfusion, first needle sharing) although this may be impractical for periods longer than 2 or 3 years. Consider testing children born to infectious women (IV, C) (Dienstag, 1997).

For other non-sexual contacts thought to be at risk, discuss with the consultant in communicable disease control or equivalent.

- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rate of transmission outside HIV co-infection (see above), monogamous partners may choose not to use them (IV, C).

Follow-up

- As for hepatitis B (IV, C)
- Immunity is probably sub-type specific only; there are at least seven sub-types. (Dore, Kaldor & McCaughan, 1997; Gretch, 1997; Lok & Gunaratnam, 1997)

Screening and primary prevention

- Consider testing for hepatitis C in all intravenous drug users, especially if equipment has been shared, in hemophiliacs or other patients who received blood or blood products pre-1990, and in people sustaining a needle-stick injury if the donor HCV status is positive or unknown (III, B) (Alter, 1997; Kaldor et al., 1992; Ramsay et al., 1998; Hamid et al., 1999; Sawayama et al., 2000; Bodsworth et al., 1996; Anon, 1993). Other groups to be considered for testing are sexual partners of HCV positive individuals, gay men, especially if HIV-infected, female sex workers, tattoo recipients, alcoholics and ex-prisoners (III, B) (Ward, Day, & Weber, 1999; Alter, 1997; Tedder et al., 1991; Bodsworth et al., 1996; Neumayr et al., 1999; Guadagnino et al., 1998; Satoglu et al., 1998; Mesquita, Granato, & Castelo, 1997; Balasekaran et al., 1999; Delage et al., 1999). It may take 3 months or more for the anti-HCV test to become positive after exposure (see "incubation period" in the original guideline document).
- Since 1990 all donated blood in the United Kingdom has been screened for HCV and all blood products rendered incapable of transmitting infection (III, B) (Regan et al., 2000).
- Needle and syringe exchange schemes have led to a fall in parenterally transmitted infections including HCV, hepatitis B virus (HBV), and HIV, although not consistently (III, B) (Hagan et al., 1999; Goldberg, Cameron, & McMenamin, 1998; van Beek et al., 1998).

Definitions

The following rating scheme was used for major management recommendations.

Levels of Evidence

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

II a

- Evidence obtained from at least one well designed controlled study without randomisation

II b

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

A (Evidence levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis, management and treatment of patients who have viral hepatitides A, B, or C
- Decreased rates of infection of viral hepatitides A, B, or C
- Decreased morbidity and mortality due to viral hepatitides A, B, or C infection and complications of infection

POTENTIAL HARMS

Not stated

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Clinical Effectiveness Group reminds the reader that guidelines in themselves are of no use unless they are implemented systematically. The following auditable outcome measures are provided:

Acute hepatitis (A, B, or C)

- Patients with acute hepatitis infection should be assessed clinically for severity, and have blood samples taken for serology, liver function, prothrombin time, and renal function, all taken on the initial visit (target >90%).
- A clear treatment and follow up plan should be stated in the notes (target 100%)

Hepatitis A

- If the clinic policy is to test and vaccinate gay men:
  - test for immunity (target >90%)
  - offer vaccination (target >90%)
- Provide written information on transmission and outcome of hepatitis A to infected patients (target >95%)

Hepatitis B

- Test patients in known at-risk groups for infection/immunity (target >90%)
- Offer vaccination to all non-immune patients at continuing risk (target >90%)

- In those offered vaccination, give a full course and test for post-vaccination response (target >50%)
- Provide written information on transmission and outcome of hepatitis B to infected patients (target >95%)
- Perform liver function tests once the diagnosis is known (target >80%)
- Write a clear long-term management plan in the notes of hepatitis B virus infected patients (target >95%)

Hepatitis C

- Ascertain the hepatitis C and B status of intravenous drug users (target >80%)
- Provide written information on transmission and outcome of hepatitis C to infected patients (target >95%)
- Perform liver function tests once the diagnosis is known (target >80%)
- Write a clear long-term management plan in the notes of hepatitis C virus-infected patients (target >95%)

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline on the management of the viral hepatitides A, B, and C. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [201 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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1999 Aug (revised 2002)

GUIDELINE DEVELOPER(S)

British Association of Sexual Health and HIV - Medical Specialty Society

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Not stated

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Conflict of Interest: None

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates a previously released version: London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in HTML format from the Association for Genitourinary Medicine (AGUM) Web site. Also available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- UK national guidelines on sexually transmitted infections and closely related conditions. Introduction. Sex Transm Infect 1999 Aug;75(Suppl 1):S2-3.

Electronic copies: Available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

The following is also available:

- Revised UK national guidelines on sexually transmitted infections and closely related conditions 2002. Sex Transm Infect 2002;78:81-2.

Print copies: For further information, please contact the journal publisher, BMJ Publishing Group.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 8, 2000. The information was verified by the guideline developer on January 12, 2001. This summary was updated again on August 5, 2002. This summary was updated most recently on November 27, 2002.

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